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Title: Activation of Aromatic C-F Bonds by a N-Heterocyclic Olefin (NHO)

Authors: Anukul Jana, Debdeep Mandal, Shubhadeep Chandra, Nicolás I. Neuman, Arighna Sarkar, Abhinanda Kundu, Srinivas Anga, Hemant Rawat, Carola Schulzke, Kaustubh R. Mote, Biprajit Sarkar, Vadapalli Chandrasekhar, and Alok Mahata

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Activation of Aromatic C-F Bonds by a *N*-Heterocyclic Olefin (NHO)

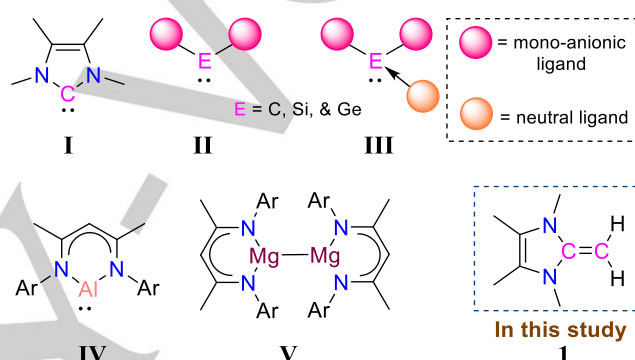
Debdeep Mandal,^[a] Shubhadeep Chandra,^{[b],[c]} Nicolás I. Neuman,^{[b],[d]} Alok Mahata,^[a] Arighna Sarkar,^[a] Abhinanda Kundu,^[a] Srinivas Anga,^[a] Hemant Rawat,^[a] Carola Schulzke,^{*,[e]} Kaustubh R. Mote,^{*,[a]} Biprajit Sarkar,^{*,[b],[c]} Vadapalli Chandrasekhar,^{*,[a],[f]} and Anukul Jana^{*,[a]}

Dedicated to Professor K. V. R. Chary on the occasion of his 65th birthday.

Abstract: A *N*-heterocyclic olefin (NHO), a terminal alkene selectively activates aromatic C-F bonds without the need of any additional catalyst. As a result, a straightforward methodology was developed for the formation of different fluoroaryl substituted alkenes in which the central carbon-carbon double bond is in a twisted geometry.

Compounds containing C-F bond(s) are extremely important in diverse fields ranging from materials chemistry^[1] to medicinal chemistry.^[2] In comparison to the C-H bond, the most striking differences of the C-F bond are its reverse polarity and higher bond energy.^[3] These features contribute to the unique physical and chemical properties of fluorinated compounds. The synthesis of such compounds and the ability to selectively activate C-F compounds in this family is an important area of research. Low-valent low-coordinate transition metal complexes have been known to activate the C-F bond by an oxidative addition.^[4] Strong Lewis acids as well as frustrated Lewis pairs (FLPs) are also known for electrophilic activation of the C-F bond.^[5] In 1998, Kuhn *et al.* reported a nucleophilic aromatic C-F activation using the *N*-heterocyclic carbene (NHC) **I** (Scheme 1).^[6] Since then, nucleophilic activation of aromatic C-F bonds have been achieved employing various two-coordinate divalent Group 14 compounds such as different NHCs, cyclic(alkyl)(amino)carbenes (CAACs), *N*-heterocyclic silylene **II**,^[7] and base stabilized three-coordinate divalent Group 14

compounds such as base stabilized silylenes and germylenes **III** (Scheme 1).^[8] Also, aromatic C-F activation has been reported using *N*-heterocyclic aluminylene, **IV**^[9] and Jones's Mg(I)-Mg(I) bonded compound, **V** (Scheme 1).^[10]



Scheme 1. Selected examples of low-valent main group compounds that activate aromatic C-F bond (Ar = 2,6-*i*-Pr₂C₆H₃).

However, all the above mentioned C-F activation of fluoroarenes are restricted in their utility for the synthesis of any general family of organofluorine compounds. This and the consideration of the lack of *direct* synthetic methodologies for an important class of compounds viz., fluoroorgano substituted (fluoro, fluoro-alkyl, fluoro-aryl) alkenes^[11] prompted us to consider a *N*-heterocyclic olefin (NHO) 1,3,4,5-tetramethyl-2-methyleneimidazoline **1** (Scheme 1).^[12] We report that this terminal alkene is an excellent reagent for the nucleophilic activation of aromatic C-F bond under the *direct* formation of different fluoroaryl substituted alkenes without using any additional catalyst. Previous syntheses of fluoroaryl substituted alkenes have been reported using transition-metal complex-catalyzed alkenylation of fluoroarenes.^[13] Very recently Berkessel and his group have reported carbene-derived pentafluorophenyl substituted alkenes using corresponding fluoroarylaldehyde as a precursor.^[14] Our method, apart from its novelty, has the advantage of being applied to a wide range of aromatic fluoro hydrocarbons, and also reveals an excellent selectivity.

[a] Dr. D. Mandal, A. Sarkar, Dr. A. Kundu, Dr. S. Anga, H. Rawat, Dr. K. R. Mote, Prof. V. Chandrasekhar, Dr. A. Jana
Tata Institute of Fundamental Research Hyderabad,
Gopanpally, Hyderabad-500107, India
E-mail: krmote@tifrh.res.in (K.R.M.); ajana@tifrh.res.in (A.J.)

[b] S. Chandra, Dr. N. I. Neuman, Prof. Dr. B. Sarkar
Institut für Chemie und Biochemie, Anorganische Chemie, Freie
Universität Berlin, Fabeckstraße 34–36, 14195, Berlin, Germany

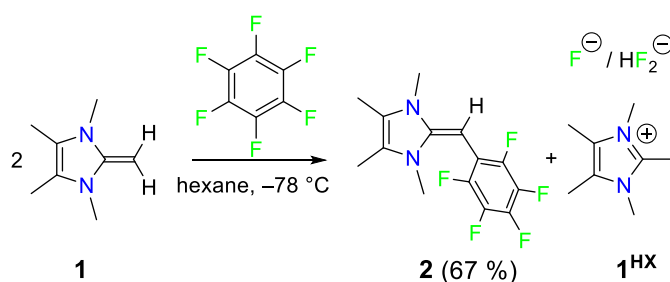
[c] S. Chandra, Prof. Dr. B. Sarkar
Institut für Anorganische Chemie, Universität Stuttgart,
Pfaffenwaldring 55, D-70569, Stuttgart, Germany
E-mail: biprajit.sarkar@iac.uni-stuttgart.de

[d] Dr. N. I. Neuman
Instituto de Desarrollo Tecnológico para la Industria Química,
CCT Santa Fe CONICET-UNL, Colectora Ruta Nacional 168,
Km 472, Paraje El Pozo 3000 Santa Fe, Argentina

[e] Prof. Dr. C. Schulzke
Institut für Biochemie, Universität Greifswald, Felix-Hausdorff-
Straße 4, D-17487, Greifswald, Germany
E-mail: carola.schulzke@uni-greifswald.de

[f] Prof. V Chandrasekhar
Department of Chemistry, Indian Institute of Technology
Kanpur, Kanpur-208016, India
E-mail: vc@iitk.ac.in

Supporting information for this article is given via a link at the end of the document.



Scheme 2. Reaction of **1** with hexafluorobenzene.

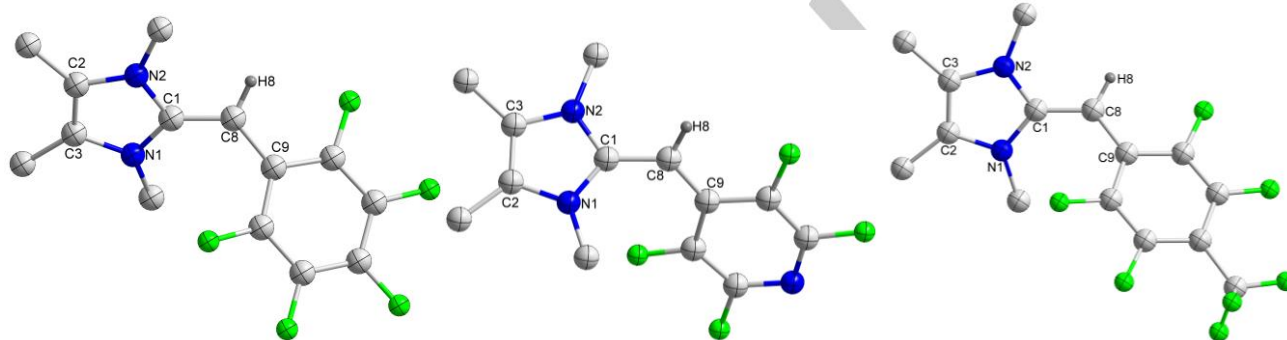


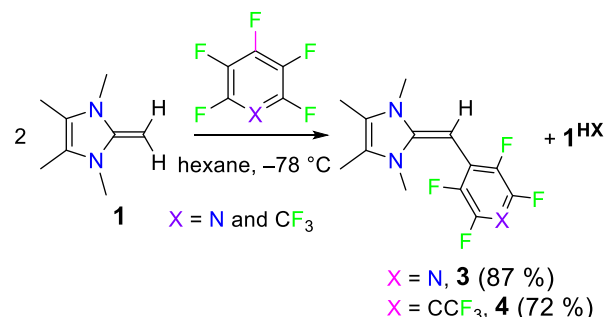
Figure 1. Molecular structures of **2** (left), **3** (middle), and **4** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8-H are omitted for clarity reasons.

The reaction of **1** with hexafluorobenzene in a 2:1 ratio in hexane, resulted in the formation of the fluoroaryl substituted alkene, i.e. a C-F activation product, **2** in 67 % yield along with the imidazolium salt, **1^{HX}** (Scheme 2).^[15] The formation of compound **2** which is air and moisture sensitive has been confirmed by the presence of three singlet resonances at 1.29, 2.42, and 3.96 ppm in a 6:6:1 ratio, respectively, in the ¹H NMR spectrum and three multiplets at -176.68, -167.05, and -149.11 ppm in a 1:2:2 ratio, respectively, in the ¹⁹F NMR spectrum. In this reaction **1** also acts as HF scavenger and forms the imidazolium salt, **1^{HX}** containing a mixture of fluoride (F⁻) and bifluoride (HF₂⁻) as counter anions.^[15] The solid state molecular structure of **2** revealed that the central C1-C8 bond distance is 1.391(16) Å (Figure 1), which is longer than the corresponding distance in **1** (1.363(3) Å)^[12] and imidazole-imidazolium-substituted alkene (1.334(5) Å for *E*-isomer and 1.322(6) Å for *Z*-isomer).^[16] The bond elongation is due to the installation of the electron-withdrawing group in place of H-substituent. The notable feature of **2** is a twist angle of 24.79(12)° around the central carbon-carbon double bond.

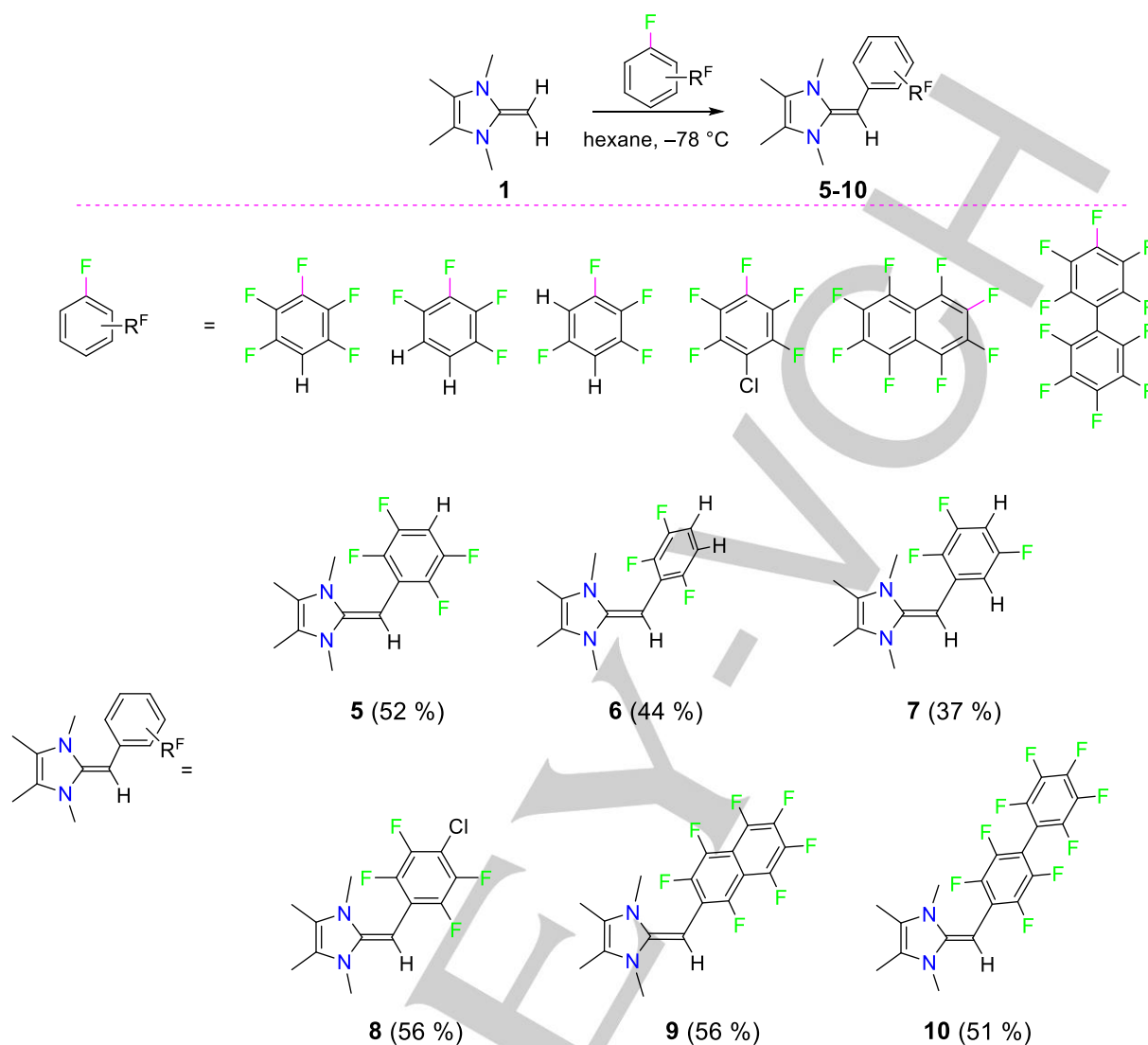
After this initial success, we considered more reactive perfluorinated arenes such as pentafluoropyridine and octafluorotoluene for reaction with **1**. The 2:1 reaction of **1** with pentafluoropyridine and octafluorotoluene gave regio-selectively the corresponding fluoroaryl substituted olefins **3** (87 %) and **4**

(72 %), respectively as deep yellow colored solids (Scheme 3).

To minimize the employed amount of **1**, we considered Et₃N as a HF scavenger. However, **1** does always compete as proton scavenger with Et₃N even when 10 equivalents of Et₃N were used.^[15] Formation of **3** and **4** were confirmed by solution state NMR spectroscopy as well as by single crystal X-ray diffraction analysis (Figure 1). The twist angle of the exocyclic olefin moiety for compound **3** is as high as 45.76(76)° which is higher than that of compound **4** (35.83(12)°) and compound **2** (24.79(12)°).



Scheme 3. Reactions of **1** with pentafluoropyridine and octafluorotoluene.



Scheme 4. Reactions of **1** with different fluoroarenes.

Subsequently, to see the regioselectivity of **1** towards the C-F activation as well as to obtain different fluoroaryl substituted olefins we have considered partially fluorinated compounds such as pentafluorobenzene, 1,2,3,4-tetrafluorobenzene, 1,2,3,5-tetrafluorobenzene, and chloropentafluorobenzene along with octafluoronaphthalene and decafluorobiphenyl (Scheme 4). The reaction of **1** with pentafluorobenzene, 1,2,3,4-tetrafluorobenzene, and 1,2,3,5-tetrafluorobenzene leads to exclusive regio-selective C-F activation products **5**, **6**, and **7**, respectively (Scheme 4). These compounds show unique ^{19}F - $^{19}\text{F}/^{19}\text{F}$ - $^1\text{H}/^1\text{H}$ - ^1H scalar-coupling network.

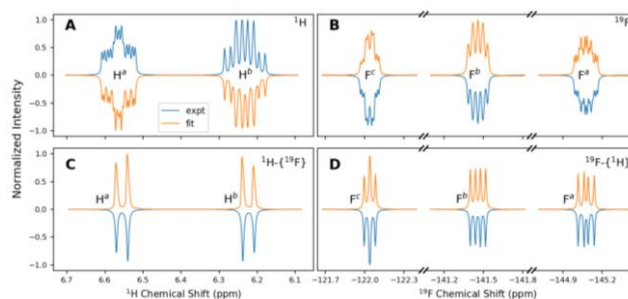


Figure 2. Experimental and simulated ^1H (A), $^1\text{H}\{^{19}\text{F}\}$ (C), ^{19}F (B), and $^{19}\text{F}\{^1\text{H}\}$ (D) NMR spectra of compound **6**.

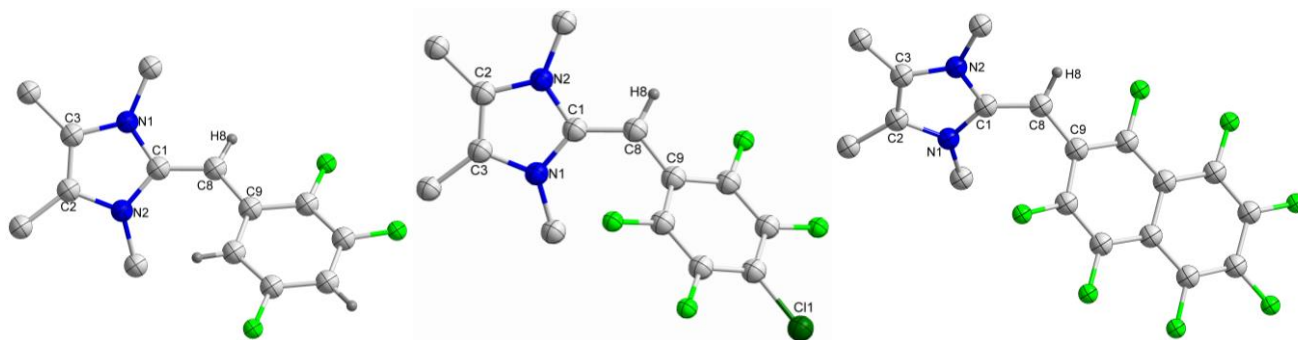
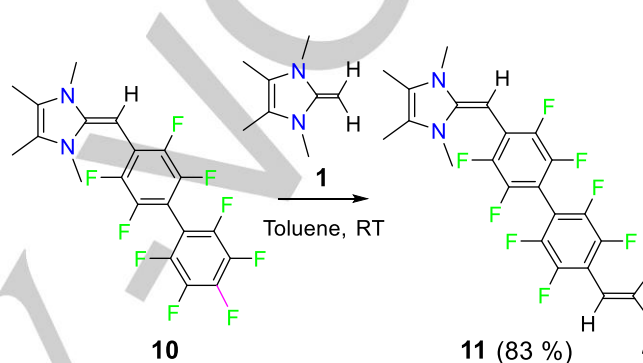


Figure 3. Molecular structures of **7** (left), **8** (middle), and **9** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8-H are omitted for clarity reasons.

In order to characterize and assign these resonances, the splitting patterns of all resonances were fitted using simulations providing values of the scalar couplings and the likely connectivity. In case of compound **6**, for instance, three ^{19}F resonances and two ^1H resonances from the fluoroaryl-substituent were unambiguously assigned using their scalar-coupling constants and the experimentally obtained ^1H , $^1\text{H}\{^{19}\text{F}\}$, ^{19}F , and $^{19}\text{F}\{^1\text{H}\}$ spectra matches well with the simulated spectra (Figure 2). The formation of compound **7** was further confirmed by its solid state molecular structure determination (Figure 3).

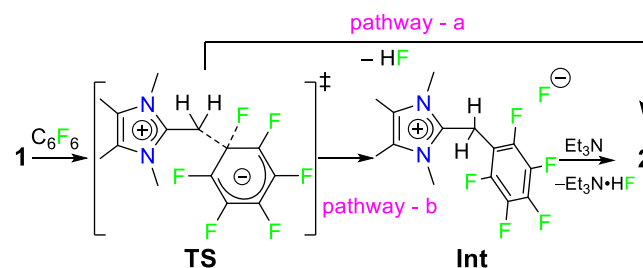
The reaction of **1** with chloropentafluorobenzene leads to selective C-F activation resulting in **8** with 56 % yield (Scheme 4). The molecular X-ray structure of **8** shows a twist angle of the exocyclic olefin moiety of only $18.34(22)^\circ$ which is more acute than that of **2** ($24.79(12)^\circ$), **3** ($45.76(76)^\circ$), **4** ($35.83(12)^\circ$), and **7** ($32.10(11)^\circ$). On treatment of **1** with octafluoronaphthalene, compound **9** was obtained in 56 % yield as a bright orange colored solid as a result of selective C2-F activation (Scheme 4). Its structural analysis exhibits a twist angle of the exocyclic olefin moiety of $24.29(16)^\circ$ (Figure 3).

The reaction of **1** with decafluorobiphenyl leads to compound **10** (Scheme 4). A small amount of the double C-F activation product **11** was also noticed, even when a strict 1:1 stoichiometry was imposed. Subsequently, the bis-alkenyl moiety functionalized octafluorobiphenyl system **11** was synthesized on purpose by reacting **10** with **1** (Scheme 5). The X-ray structural analyses reveal twist angles of the exocyclic olefin moieties of $34.79(11)^\circ$ in **10** and of $26.74(19)^\circ$ and $32.34(17)^\circ$ in **11** (Figure 4).



Scheme 5. Synthesis of **11**.

We propose that the reaction of **1** with fluoarenes proceeds through an aromatic nucleophilic substitution reaction (Scheme 6). A nucleophilic attack of **1** at the electrophilic C-centre of the C-F moiety of fluoroarenes leads to a transition state, **TS**. This **TS** can directly lead to the product **2** by an elimination of HF (pathway - a) or it can evolve into an ionic intermediate (**Int**, $[\text{2H}^+\text{F}^-]$), which has different fates depending on the conditions (pathway - b).



Scheme 6. Proposed mechanism of aromatic C-F bond activation by NHO, **1**.

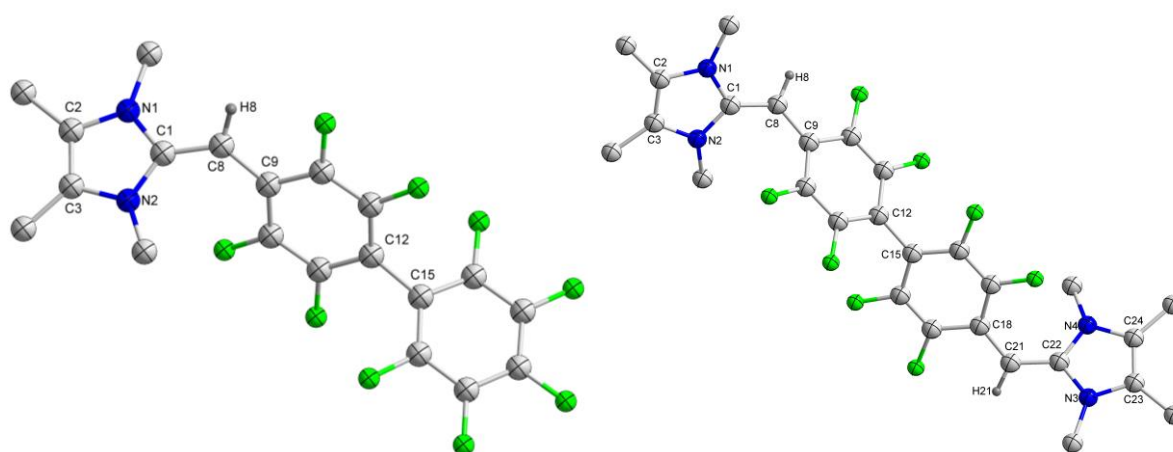


Figure 4. Molecular structures of **10** (left) and **11** (right) with thermal ellipsoids at 50% probability level. All H atoms except C8–H (for **10**) and C8–H and C21–H (for **11**) are omitted for clarity reasons.

One of the observed routes is subsequent elimination of HF leading to **2**. This route was computationally observed when a relaxed surface scan starting with **1** + C₆F₆ was performed in hexane as pseudo solvent, without inclusion of additional molecules. In this case **Int** was not the final structure, but **2** + HF (pathway - a). **Int** could be stabilized if a molecule of Et₃N was added, leading to deprotonation of [2H⁺], through TS^{Et₃N}, and final products **2** + Et₃N•HF (pathway - b and see Figure S51 in Supporting Information). This proposed pathway is supported by the theoretical calculation at PBEO/def2-TZVP level of theory.^[15] The energy barrier of **TS** in hexane is 22.1 kcalmol⁻¹ whereas the formation of **2** is exergonic by ΔG₃₀₀ = -21.7 kcalmol⁻¹ (Figure 5).^[15] **Int** could also be stabilized if DMF was chosen as pseudo solvent in the calculations (pathway - b), which also resulted in a slight lowering of the activation barrier to 21.3 kcalmol⁻¹ (see Figure S50 in Supporting Information).

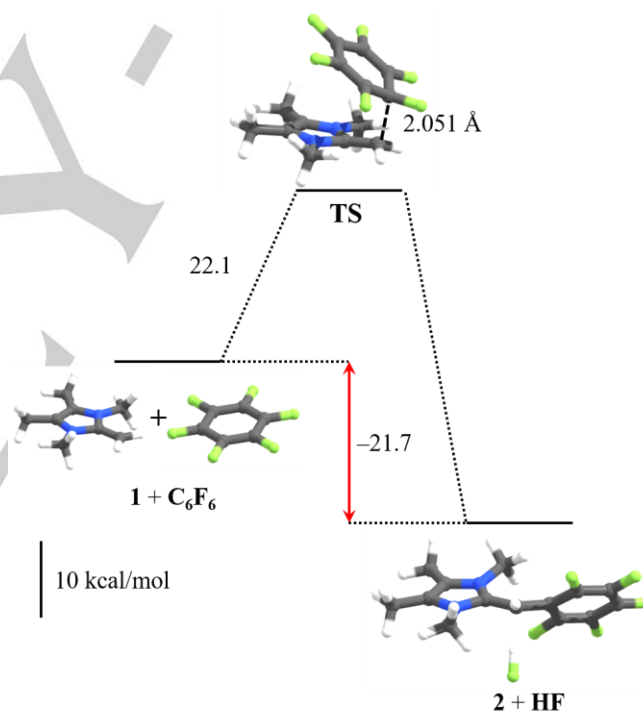


Figure 5. The reaction energy profile diagram for the C-F bond activation of C₆F₆ by **1** (all energy values are in kcalmol⁻¹).

In conclusion, we have demonstrated that the *N*-heterocyclic olefin (NHO), as a terminal alkene selectively activates a large variety of aromatic C-F bonds without any additional catalyst. The aromatic C-F activation by NHO results in a straightforward formation of fluoroaryl substituted alkenes, which have a twisted central carbon-carbon double bond with an angle varying from 18.34° to 45.76°, depending on the fluoroaryl substituent. Considering that a large variety of NHOs are already available,^[17] and that new NHO designs can be readily adapted

to our strategy, our reported synthetic methodology is extremely versatile.

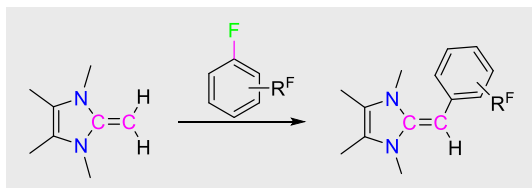
Acknowledgements

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Keywords: alkenes • C-F activation • fluorine • N-heterocyclic olefins • nucleophilic substitution

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Herein we report the activation of aromatic C-F bonds by *N*-heterocyclic olefin (NHO) without the need of any additional catalyst. As a result, a straightforward methodology was developed for the formation of different fluoroaryl substituted alkenes.

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